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Are airways structural abnormalities more frequent in children with recurrent lower respiratory tract infections?

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Summary
We report bronchoscopic changes observed in children with recurrent lower airways infections (RLAI) and findings in control children undergoing bronchoscopy for causes other than RLAI.
Patients and methods: Retrospective case-control cohorts study. The clinical records of children who had fiberoptic bronchoscopy (FB) for a history of RLAI without any known underlying disorder between 2007 and 2013 and of control children who required FB for other causes were reviewed. Clinical features, bronchospic findings and bronchoalveolar lavage (BAL) results were assessed.
Results: Cases were 62 (32 female) children aged 5 years (1–12) and controls 29 children aged 4.5 years (0.5–14). Airway malacia was observed in 32 (52%) vs 4 (13%) ($p = 0.001$), profuse respiratory secretions in 34(55%) vs 6 (20%) ($p = 0.007$). Endobronchial obstruction: 4 (6.4%) and tracheobronchomegaly were observed only in cases. In cases with profuse respiratory secretions there was a higher prevalence of airways malacia: 64.7% vs 35.7% ($p = 0.04$) and of positive BAL cultures: 45.5% vs 13.3% ($p = 0.04$). Isolated organisms in cases were non-typable *Haemophilus influenzae* and *Streptococcus pneumoniae* most frequently. *Pneumocystiis jirovecii*, *Staphylococcus aureus*, and *Streptococcus mitis* were isolated in controls.
Conclusions: Half of the children with RLAI had tracheo and/or bronchomalacia, their frequency being in keeping with previous reports and far higher than that observed in controls. It was associated with profuse respiratory secretions and with a higher frequency of positive BAL cultures mostly for non typable *H. influenzae* and *S. pneumoniae* which were not isolated in controls.

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Introduction

Recurrent lower airways infections involve the pulmonary parenchyma and or the lower airways. Although the scope of the term can greatly vary depending on the kind and number of episodes that are included, their incidence in childhood has been estimated to be about 7% [1]. Their clinical presentation ranges from episodes of persistent bacterial bronchitis (PBB) and or recurrent pneumonia, to chronic suppurative pulmonary disease with or without bronchiectasis [2]. Inflammation-infection vicious circles, and colonization of the lower airways with organisms coming from the upper airways, owing to disturbed mucociliary clearance are thought to underlie their pathogenesis [3]. Disturbed mucociliary clearance is generally secondary to viral infections and inflammatory damage, but occasionally is caused by congenital conditions (cystic fibrosis, primary ciliary dyskinesia, inmunodeficiency…). Once non-invasive approaches to diagnosis have failed, FB is often considered for cases with either severe or protracted symptoms and in patients with associated conditions, in order to obtain biological samples and to rule out airways structural abnormalities. Airways malacia is a structural and functional weakness of the tracheal and/or bronchial walls due to cartilaginous rings abnormalities, or increase in the length of the posterior fibromuscular walls. It gives rise to complete or partial dynamic collapse of the airways lumen, hampering cough effectiveness and interfering with mucociliary clearance, leading to plugging of the airways with bronchial secretions [4]. While the incidence of malacia has been reported to be 1 in 2100 newborns [5], it is probably higher among children with RLAI [6–8]. The scarcity of reports of bronchoscopic findings in control healthy children because of the ethical problems of performing an invasive procedure in such a population prevents comparing their incidence of malacia with that found in children with RLAI. The aim of our study was to describe the bronchoscopic changes in children with RLAI, to investigate the prevalence of lower airways malacia as compared with previous reports, and to assess their prevalence in a control group of children having bronchoscopy for causes other than RLAI.

Patients and methods

Retrospective case–control cohorts study. The clinical features, bronchoscopic findings and the BAL results of children referred for FB for a history of RLAI between 2007 and 2013, and of control children who required FB for other causes were assessed.

Patients were considered to have RLAI if they had any of the following: recurrent pneumonia (2 or more in a year or 3 or more at any time), chronic wet or productive cough for over 4 weeks, persistent atelectasis (for over 3 months), or bronchiectasis (bonchial/arterial diameter ratio over 1–1.5 on chest CT scans). Children with associated conditions such as bronchopulmonary dysplasia, prematurity, difficult to control asthma, cystic fibrosis, immunodeficiency, genetic syndromes, neuromuscular, CNS or heart disease, airways or digestive tract malformations, severe scoliosis, protracted endotracheal intubation, tracheotomia or endobronchial aspiration syndromes were excluded. A control group of children without a history of RLAI who had FB for other causes over the same time span and fulfilled the same exclusion criteria were also studied. Age, sex, clinical presentation, duration of the symptoms, FB/BAL results and final diagnosis were all recorded.

FB (Olympus videobronchoscope) were performed at the Pediatric Intensive Care Unit on spontaneous breathing under sedation-analgesia and local anesthesia. Images were video recorded and reviewed later. BAL was performed at either the right middle or right lower lobes, by infusing and suctioning 0.9% saline. Recovered samples were shipped to the laboratory and studied according to the microbiology&pathology BAL protocol followed in our Hospital. A CFU count over 10^4 was considered as consistent with bronchopulmonary infection. Any growth of normal oropharyngeal organisms was disregarded. Airways malacia was considered to be present in the face of an over 50% dynamic collapse of the airways lumen during expiration on spontaneous breathing or during cough, while no suctioning was being applied [8]. Its severity was classified as mild if $<$ 70%, moderate if $\geq$ 70 $<$ 90% and severe if $\geq$ 90%. Bronchial stenosis was diagnosed when bronchial opening was either absent or severely decreased after applying mild suctioning as compared with that observed in neighboring bronchi. An observed increased amount of respiratory secretions was the only change considered to be consistent with bronchitis.

Statistics were performed by using SPSS software for Windows, version 11,0 (SPSS Inc., Chicago, IL, USA). Numeric variables were expressed as medians and the distribution of category variables as frequencies and percentages. Differences between groups were assessed using Chi square, Student t, and Mann Whitney analysis. A p value <0.05 was considered to be significant.

Results

Cases were 62 children (34 female) [aged 60.5 months (12–144)]. Sixty (96.6%) were scheduled for FB from our outpatient clinic [twenty-eight (45%) had been seen previously at four different Pediatric Chest Medicine Hospital Departments] and two had the procedure after they were admitted for an exacerbation of their respiratory symptoms. Forty-five (72.5%) had wet/productive cough, thirty-eight (61.3%) recurrent pneumonia, fifteen (24.2%) atelectasis and thirteen (21%) bronchiectasis. Twenty-nine (47%) had both chronic wet/productive cough and recurrent pneumonia. Duration of symptoms was 24 (4–60) months. A chest CT scan had been done in 32 (56%) showing abnormalities in 27 (84%): bronchiectasis 13 (48%), consolidation 7 (26%), bronchial stenosis 3 (11%) and other (cavitation, granuloma, tracheal deformity, or bilateral interstitial pattern) in 4 (14.8%).

Forty-two (67.7%) had airways abnormalities at FB: malacia 32 (51.6%) [tracheomalacia 12 (19.4%), tracheobronchomalacia 11 (17.7%), bronchomalacia 9 (14.5%)], bronchial stenosis 12 (19%) 4 of them with associated bronchomalacia, and other abnormalities 5 (8%)

[malignant glomic tumor, tuberculous granuloma, inflammatory granuloma, foreign body and tracheobronchomegaly (Mounier-Kuhn syndrome)]. Malacia was moderate in 18 (56%), severe in 11 (34%), and mild in 3 (10%). In thirty-four (54.8%) profuse respiratory secretions were observed. BAL was performed in 48 (77.4%) and one or more potentially relevant organisms were grown in 17 (35.4%): non-typable *Haemophilus influenzae* (13), *Streptococcus pneumoniae* (4), *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* y *Streptococcus viridans*. Observed signs of bronchitis had 88% sensitivity, 42% specificity, 86.6% negative predictive value and 45.4% positive predictive value for positive BAL cultures. Children with bronchitis had more frequently positive BAL cultures: 45.5% vs 13.3% ($p = 0.04$) and lower airways malacia: 64.7% vs 35.6% ($p = 0.04$).

Controls were 29 children (14 female) [aged 54 months (5—168)]. Twenty (69%) had FB in the course of a hospital admission and nine (31%) were scheduled from outpatient clinics. Twenty-two (77%) had pneumonia poorly responsive to therapy, five (17%) not confirmed suspected endobronchial foreign body inhalation, and one each hemoptysis and massive atelectasis. Ten (33%) had underlying oncological conditions and one each were later diagnosed of pulmonary alveolar proteínosis and idiopathic pulmonary hemosiderosis. Six (21%) had lower airways abnormalities at FB malacia 4 (13%) [tracheobronchomalacia 1 (3%) and bronchomalacia 3 (10%)], bronchial stenosis 4 (13%) (2 each had associated bronchomalacia and bronchitis). Six (20%) had evidence of bronchitis (3 of them with associated bronchomalacia). BAL was performed in 17 (58%) and three potentially relevant organisms were grown in two of them: *Pneumocystiis jirovecii*, *Streptococcus mitis*, and *S. aureus*. Differences between groups are shown on Table 1.

This study was approved for its publication by the Clinical Research and Ethics Committee at Cruces Hospital University.

Discussion

Cases were all children with long-standing symptoms of RLAI who had FB in order to examine their airways and to assess endobronchial inflammation and infection. Associated conditions which might underlie the symptoms were excluded. The yield of FB in children with RLAI has been reported to be high. Chang et al. [10], found structural airways abnormalities in 39.7% of children with chronic suppurative pulmonary disease. Kompare et al. [7] reported lower airways malacia in 74% of children with PBB, and Douros et al. [11] found bronchial inflammation and positive BAL cultures in 97.8% and 74.2% respectively of children with chronic wet/productive cough. Likewise FB in our study had a high return: nearly seven out of ten cases (68%) had structural airways abnormalities and over half (55%) had evidence of bronchitis, with half of the latter having bacterial bronchial infection.

Table 1 Patients and bronchoscopic findings.

	Cases	Controls	*p*
Total number (female)	62 (34)	29 (14)	—
Median age (month)	60.5 (12—144)	54 (5—168)	0.2
Airways abnormalities No. (%)	42 (68)	6 (21)	0.001
Malacia	32 (52)	4 (13)	0.009
Bronchial stenosis	12 (19)	4 (13)	0.2
Other abnormalities	5 (8)	—	—
Bronchitis No. (%)	34 (55)	6 (20)	0.007

Chronic wet/productive cough has a high sensitivity - albeit low specificity — for bacterial bronchial infection [12]. It was the commonest presentation, being present in 3 out of 4 cases. Most of them (67%) had associated recurrent pneumonia, which might have been caused by spread of chronic endobronchial infection to neighboring lung parenchyma. It could be speculated that according to the "vicious circle hypothesis", cases spanned different stages of chronic bacterial endobronchial infection: from PBB, to chronic suppurative pulmonary disease with or without bronchiectasis [3]. Inappropriate recognition and early treatment of this condition could lead to persistent neutrophil-dominated airways inflammation in susceptible children [13] and ultimately to the development of bronchiectasis. The latter were already present in one out of five cases.

We considered the evidence of profuse respiratory secretions as an indication of bronchitis (Fig. 1a), as it has been previously shown to correlate with endobronchial infection [14]. Other abnormalities like erythema or edema could be elicited by the same bronchoscopic procedure and thus more difficult to be interpreted. Bronchitis had both high sensitivity and high negative predictive value for positive BAL cultures in our series. It was present in over half of the cases, and 45% of them had evidence of endobronchial infection, despite FB being done while most of the patients scheduled from outpatient clinics departments were in their usual "baseline" condition. Eight of ten isolated organisms belonged to the two main bacterial species which commonly colonize the oro-rhinopharinx, and are usually responsible for chronic respiratory infections: non-typable *H. influenzae* and *S. pneumoniae*. These organisms which were not isolated in controls cause disease when they get down into the lower airways due to disturbed defense mechanisms, and they can form slow-growing biofilms making their eradication very difficult [15]. It is noticeable the high prevalence in our cases of non-typable *H. influenzae* infection. Arguably the extension of the conjugated pneumococcal vaccine might underlie a decreased incidence of bronchial infection with this organism, as it has been reported in otitis media, and conversely a comparative rise in non-typable *H. influenzae* strains which are not included in the conjugated *H. influenzae* vaccine [16].

Tracheal and or bronchial malacia were the commonest structural abnormalities observed in our cases (Fig. 1(a and b)). As there are no precise objective diagnostic criteria for these conditions to be used in everyday clinical practice, we have relied on the comparatively subjective assessment of an over 50% collapse of the airways lumen during cough and/or tidal breathing as reported by Wittenborg et al., in 1967 based on healthy children tracheograms [9]. Half of our cases had lower airways

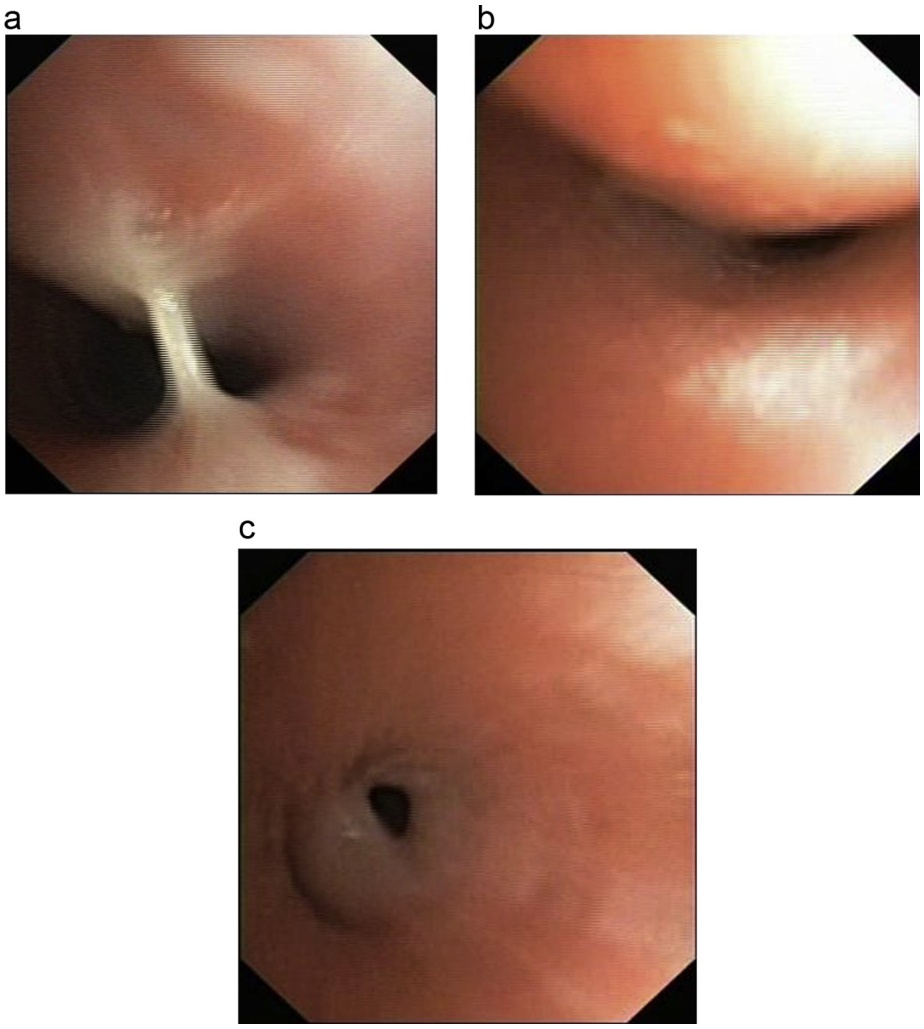

Figure 1 Profuse secretions and additional tracheomalacia both at inspiration (a) and expiration (b), and lingular bronchial stenosis (c) in a ten-year-old girl with chronic wet cough, recurrent pneumonia and cylindrical bronchiectasis at both lower lobe bronchi on chest CT scan.

malacia, mostly tracheomalacia, and airway lumen collapse was over 80% in nine out of ten. Our observed frequency is higher than the 33% reported by Marchant et al. [17] in children of median age 2.6 years with chronic wet/productive cough and lower than the 72% reported by Kompare et al. [7] in children younger than 5 with PBB. Airways dynamic collapse during expiration (Fig. 1(b)) allegedly interferes with lower airways secretions clearance leading to plugging, further impairment of mucociliary clearing and persistent bacterial endobronchial infection. Lower airways malacia was associated both with bronchitis and bacterial endobronchial infections as previously reported [18]. This association does not prove malacia to be the cause, and bronchial inflammation could in some cases be the primary event leading eventually to lower airways malacia [10].

Reported studies are biased by the lack of control groups of healthy children on ethical grounds as FB is an invasive procedure, and thus we do not know what the prevalence of lower airways malacia is in such a population. It is well known that most if not all of children with tracheo bronchial fistula have associated tracheomalacia, albeit only 10%—20% have significant respiratory symptoms [19]. It could be speculated that to some extent the same thing might occur in healthy children, some of them having clinically silent lower airways malacia. Our control group was composed by children without a history of RLAI but who required FB by either acute or subacute respiratory symptoms. Their prevalence of lower airways malacia was significantly lower with just one having tracheomalacia, but still was far higher than that previously estimated as probably occurring in normal population [5]. One could wonder if it was caused by airways inflammation in these cases but previous clinically silent malacia cannot be ruled out. Just as lower airways malacia, bronchial stenosis (Fig. 1(c)) has been previously been linked with lower airways inflammation and bronchoscopic findings of bronchial stenosis and chest CT scans changes have shown a good correlation [11]. Its prevalence in our series was low and unassociated with either lower airways malacia or bronchitis, and did not differ between groups. We could not correlate it with the chest

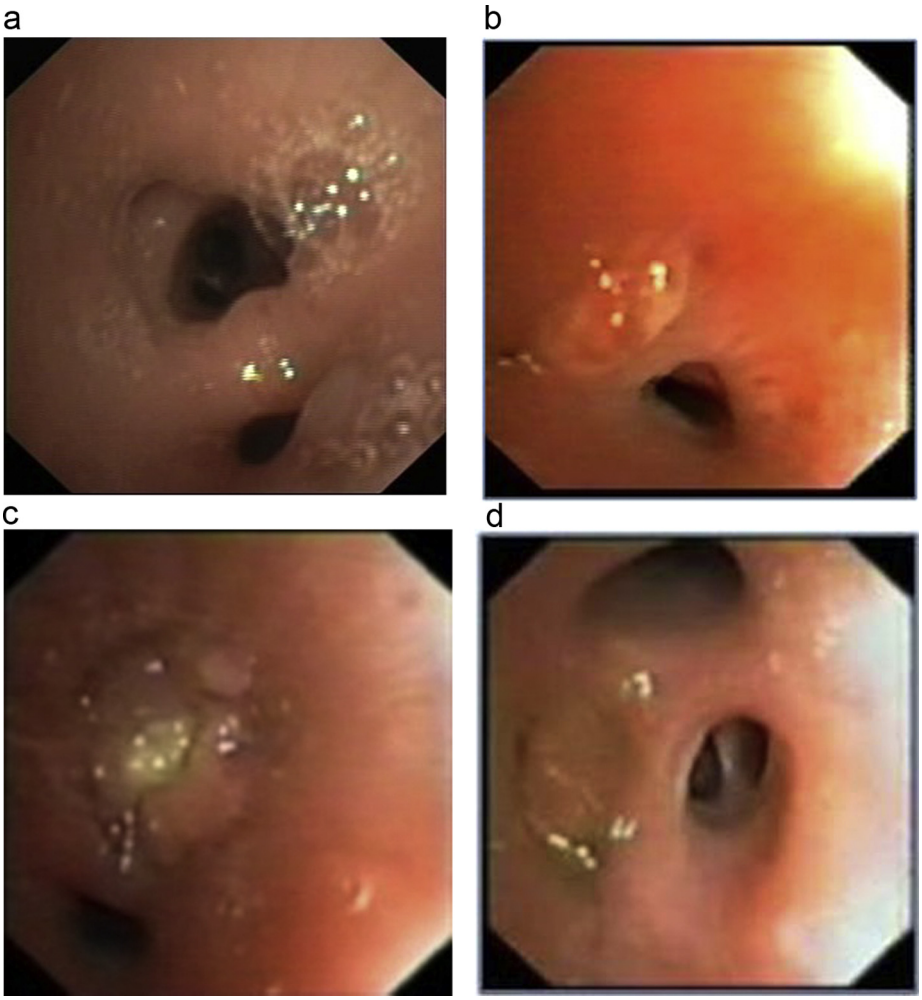

Figure 2 Obstructive lesions. Granuloma at the middle lobe bronchus in a two-year-old boy with chronic wet cough, recurrent pneumonia and BAL culture positive for *Haemophilus influenzae*. The biopsy showed reactive inflammatory changes (a). Middle lobe endobronchial tuberculous changes in a four-year-old boy with chronic wet cough and persistent atelectasis. Tuberculin skin test was positive and gastric juice culture was positive for *Mycobacterium tuberculosis* (b). Foreign body at the right lower lobe in a two-year-old girl with chronic wet cough and persistent consolidation on chest X rays (c). Endobronchial mass (malignant glomic tumor) at the right upper lobe in a twelve- year-old boy who presented with chronic wet cough and persistent consolidation on chest X rays (d).

CT scans changes, as the latter were not available in all of the cases.

Patients with other findings together made up a sizeable group. Obstructive lesions (foreign body, tuberculosis, inflammatory granuloma or endobronchial tumor) were observed in 6% of the cases (Fig. 2). These conditions may present with either chronic cough or recurrent pneumonia, although signs of persistent obstruction at one or more segmental bronchi, and chest-X rays changes (consolidation or atelectasis) may suggest the diagnosis [1]. Tracheobronchomegaly (Mounier-Kuhn syndrome) is an exceedingly rare condition during childhood which can present with chronic wet/productive cough, bronchiectasis, and striking enlargement of the transversal diameter of the trachea and main bronchi on chest X-rays, chest CT scans, and FB. It is probably underdiagnosed (Fig. 3).

Our study, being retrospective has major shortcomings. BAL was not always performed, and neither PCR for respiratory viruses nor cytology examinations were generally done, thus the possible role of respiratory viruses and the type of airways inflammation could not be assessed. We do not know how many patients were given antibiotics during the days prior to FB and if that could be associated with negative BAL cultures. Our control group does not stand for normal healthy children population.

We conclude that FB in selected children with RLAI had a high yield as structural abnormalities were observed in seven out of ten and over half had evidence of bronchitis. The commonest abnormality was lower airways malacia, mostly tracheomalacia which was observed in half, its incidence being in keeping with that previously reported and far higher than that observed in the control group. It was associated with bronchitis and endobronchial infection with non-typable *H. influenzae* and *S. pneumoniae*, these organisms not being isolated in any of the controls.

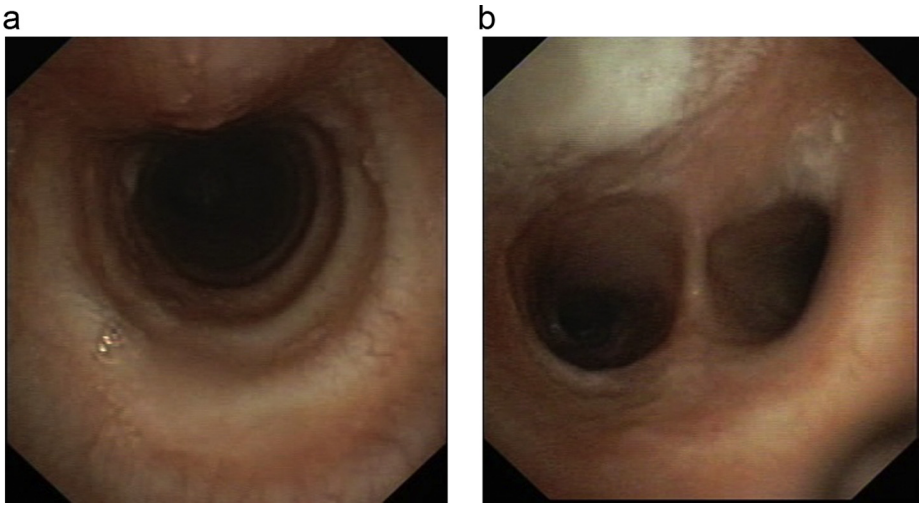

Figure 3 Mounier-Kuhn syndrome: tracheomegaly (a) and right main bronchus bronchomegaly (b) in an eleven-year-old boy with a history of daily wet cough for two years. A chest CT scan showed cylindrical bronchiectasis at both lower lobes bronchi and a diverticulum at the right main bronchus. BAL culture was positive for non-typable *Haemophilus influenzae*, *Streptococcus pneumoniae* y *Moraxella catarrhalis*.

Conflict of interest statement

The authors declare no conflict of interest.

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